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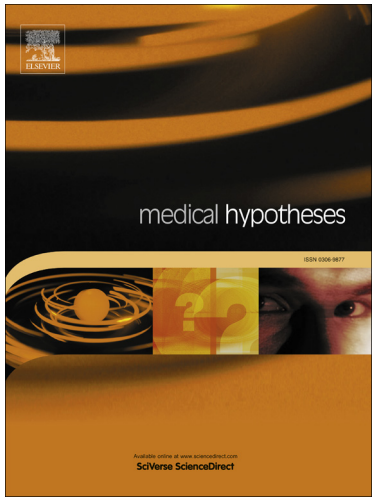


Correspondence

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Letter

**Recently discovered properties of aspirin may be doubly helpful in bipolar disorders**

Running title : aspirin in bipolar disorders

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Dear editor,

While aspirin is an ancient folk remedy sold over-the-counter for more than a century and since used in a lot of disorders, new properties of aspirin are still discovered to this day.

Aspirin may be doubly helpful in bipolar disorder. First, bipolar disorder may be the result of a pre-inflammatory multisystemic disorder[1] that affects not only mood regulation but also cardiovascular status. Patients with bipolar disorder may hence be seen as a population at intermediate risk for cardiovascular disease, and aspirin may be helpful in primary prevention in this population. However trials are warranted to confirm the benefit of aspirin in this indication [5].

Second, new properties of aspirin have been recently discovered, especially anti-inflammatory properties, which may be particularly interesting in bipolar disorder that is strongly associated with immunologic and inflammatory dysfunctions [6]. If bipolar disorders may result in some cases in a chronic inflammation of central nervous system (CNS) (due to microglia activation), fixing this inflammation may thus improve mood symptomatology and possibly prevent cognitive decline associated with this disorder. ASA is 50 to 100-fold more potent in inhibiting platelet cyclooxygenase 1 (COX-1) than monocyte cyclooxygenase 2 (COX-2) activity [2]. Choi et al [3] proposed in a recent review to reconsider the prevailing hypothesis that, by being the isoform induced in response to inflammatory stimuli, COX-2 is the most appropriate pharmacological target for anti-inflammatory therapy, and suggested that COX-1, owing to its predominant localization in microglia, is the major player in mediating the inflammatory response. It has even been suggested that mood stabilizers and antidepressive agents may improve depressive symptomatology by the inherent anti-inflammatory properties of some of them.

Preliminary data obtained in bipolar disorders suggest beneficial effects on depressive symptoms that are improved using aspirin (acetyl salicylic acid (ASA)) in low doses (in which ASA would inhibit COX-1 but not COX-2)..

In a large pharmaco-epidemiological study, Stolk et al [4] tested in 5145 patients receiving lithium whether non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids would improve bipolar symptoms (based upon the assumption that lithium treatment is relatively specific to individuals with bipolar disorders). The

main outcome measure was a calculated incidence density of medication events (change in the type or numbers of psychotropic medications prescribed or increase (>30%) in the psychotropic drug dose). Subjects receiving low-dose (≤80 mg/day) aspirin were 17% less likely to have a medication event, a finding that remained significant after adjusting for age, sex, chronic disease score and healthcare utilization. Aspirin and lithium may also exert synergistic effects in forming anti-inflammatory brain metabolites [4]. These preliminary observations thus appeared consistent with the hypothesis that COX-1 inhibitors can reduce neuro-inflammatory processes with consequent beneficial improvement of bipolar illness.

It was relatively recently discovered that aspirin administration triggers the biosynthesis of the so-called aspirin-triggered lipoxins (ATLs) (the term "lipoxin" is an acronym for lipoxygenase interaction products). Lipoxins and ATLs are generated from arachidonic acid and are considered to act as ‘braking signals’ in inflammation, dampening the second-phase inflammatory response via the modulation of microglia [7]. Microglia are considered the "resident macrophages" of the brain and play an essential role in innate immunity, homeostasis, and neurotropic support in the central nervous system. Microglia perform routine maintenance and immune surveillance in their resting state. Once activated, either by injury or an immune stimulus, microglia secrete a variety of pro-inflammatory molecules that may cause neurodegeneration if their up-regulation lasts for an extended period of time [8]. Aspirin also modulates innate and adaptive immune responses : aspirin can suppress the lymphocyte B antibody-mediated humoral immune response, as well as the neutrophil and monocyte/macrophage-mediated innate immune responses (by decreasing inter alia neutrophil cells' extravasation and their adherence to the endothelial lining, a distinctive step in the innate immunity) (for a complete review, see [9]). In addition to its strictly speaking anti-inflammatory and immune properties (that are also neuroprotective), aspirin was found to enhance adenosine production [10], to modulate nitric-oxide synthesis [11] and to inhibit nuclear factor-kappa B (NF-kB) transcriptional pathway [12], all these mechanisms potentially play a role in its neuroprotective properties.

Basselin et al demonstrated that aspirin extinguishes CNS inflammation at low and high therapeutic doses in rats [13]. In humans, the anti-inflammatory properties of low doses of aspirin have also been demonstrated in a population of subjects with

metabolic syndrome (that is frequently comorbid with bipolar disorders) : 100-300 mg/d aspirin decreased blood levels of Tumor Necrosis Factor alpha (TNF-alpha), Interleukine 6 (IL-6) and high sensitivity C-reactive protein (hs-CRP), three major inflammatory markers that have been found to be disturbed in patients with bipolar disorders [14] .

Aspirin may be doubly helpful in bipolar disorders, for prevention of cardiovascular events as well as an anti-inflammatory drug that may influence and protect the central nervous system.

Conflicts of interest : All authors declared no conflict of interest in the last 2 years.

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